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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,240	07/18/2003	George Tzertzinis	NEB-208/9-US	3580
28986	7590	04/04/2006	EXAMINER	
HARRIET M. STRIMPEL; NEW ENGLAND BIOLABS, INC. 240 COUNTY ROAD IPSWICH, MA 01938-2723			POPA, ILEANA	
			ART UNIT	PAPER NUMBER
			1633	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/622,240

Applicant(s)

TZERTZINIS ET AL.

Examiner

Ileana Popa

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-47 is/are pending in the application.
- 4a) Of the above claim(s) 3,8,10,15,19 and 21-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-7,9,11-14,16-18,20 and 47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 July 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicants' election without traverse of the invention of Group I, claims 1-20 and 47, drawn to a method of producing an hsiRNA mixture in the reply filed on 02/27/2006 is acknowledged. Applicants' election without traverse of the species of a range of 0.0125:1 to 10:1, manganese, less than 6 hours, substantial portion greater than about 50%, and about 50% of fragments capable of causing cleavage of the mRNA, is also acknowledged.

Applicants withdrew claims 21-46.

Claims 3, 8, 10, 15, and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 4-7, 9, 11-14, 16-18, 20, and 47 are pending.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the instant application by number and filing date.

Drawings

4. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Fig. 6A is not of sufficient quality. Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 4-7, 11, 13, 14, 16-18, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Zamore et al. (Cell, 2000, 101: 25-33).

Zamore et al. teach generation of a mixture of 21 to 23 nucleotides long hsiRNAs by incubated a large dsRNA having one strand complementary to a target mRNA in *Drosophila* lysate, in the presence of the target mRNA (i.e., the reaction mixture contains a divalent transition metal cation and RNase III) (p. 27, column 2 bridging p.30,

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and p. 32, column 2, first paragraph); the hsRNA mixture thus generated represents a substantial portion of the long dsRNA sequence, and it is capable to bind specifically to and cleave the target mRNA (p. 26, column 1, fourth paragraph). With respect to the limitations of the divalent transition metal being manganese at a concentration of about 5-10 mM or 10-20 mM, absent evidence to the contrary, the lysate of Zamore et al. comprises manganese at these concentrations. With respect to the limitation of a ratio of RNase III to large dsRNA being in a range of about 0.0125:1 to 10:1, absent evidence to the contrary, the reaction mixture of Zamore et al. comprises a ratio of RNase III to large dsRNA in that range. With respect to the limitation of the mixture comprising 18-25 bp fragments in a proportion greater than 30%, absent evidence to the contrary, Zamore's mixture of hsiRNAs comprises more than 30% hsiRNA that have this length. Since the art teaches a method of producing an hsiRNA mixture by digesting a preparation of large dsRNA in a reaction mixture containing Rnae III and manganese, wherein the hsiRNA mixture is the product of digestion of the dsRNA in fragments of about 15-30 nucleotides capable to specifically bind to and cleave the target mRNA, the claimed invention is anticipated by the above-cited art.

4. Claims 1, 2, 4-7, 9, 12, and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Beach et al. (Pub. No.: 2002/0162126), as evidenced by Ketting et al. (Genes & Development, 2001, 15: 2654-2659).

Beach et al. teach generation of a mixture of hsiRNAs by introducing into a cell expressing Dicer (i.e., a RNase III, see Ketting et al.), a large dsRNA comprising a

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nucleotide sequence complementary to a target nucleotide sequence, wherein the presence of the mixture of hsiRNAs results in silencing of the target gene (p.1, column 2, paragraphs 007-0013, and p. 2, paragraph 0017). Beach et al. also teach that Dicer produces fragments at least 20 to 22 nucleotides in length (p. 2, paragraph 0017). With respect to the limitations of the divalent transition metal being manganese at a concentration of about 5-10 mM or 10-20 mM, absent evidence to the contrary, the cell of Beach et al. comprises manganese at these concentrations. With respect to the limitation of a ratio of RNase III to large dsRNA being in a range of about 0.0125:1 to 10:1, absent evidence of the contrary, the reaction mixture of Beach et al. comprises a ratio of RNase III to large dsRNA in that range. With respect to the limitation of complete digestion in less than 6 hours, again, absent evidence to the contrary, the dsRNA of Beach et al. is completely digested inside the cell in less than 6 hours. Since the art teaches a method of producing an hsiRNA mixture by digesting a preparation of large dsRNA in a reaction mixture containing RNase III and manganese, wherein the hsiRNA mixture is the product of complete digestion of the dsRNA in fragments of about 15-30 nucleotides in less than 6 hours and wherein the presence of the mixture inside the cells results in target gene silencing, the claimed invention is anticipated by the above-cited art.

5. Claims 1, 2, 4, 9, 11-14, 16-18, 20, and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Yang et al. (Pub. No.: US 2004/0014113).

Yang et al. teach a method of producing a mixture of hsiRNA fragments comprising 15-30 nucleotides by digesting a large dsRNA, having a sequence complementary to a target mRNA, with *E. coli* RNase III; the hsiRNAs mixture represents is complete in less than 6 hours and represents a set of overlapping fragments, wherein at least one fragment, or 50 to 100 % are capable to cleave the target mRNA when introduced into an eukaryotic cell (p. 1, paragraph 004, p. 2, paragraph 0015, p. 6, paragraph 0045, p. 6 paragraph 0053, Fig. 1B). The ratio of RNase III to dsRNA is in the range of about 0.0125: 1 (p. 8, paragraph 0079). Yang et al. teach reaction conditions that efficiently generate 20-25 bp siRNAs, i.e., more than 30% (p. 2, paragraph 0015). With respect to the limitation to Since the art teaches a method of producing an hsiRNA mixture by digesting a preparation of large dsRNA in a reaction mixture containing RNase III, wherein the hsiRNA mixture is the product of complete digestion of the dsRNA in fragments of about 15-30 nucleotides in less than 6 hours and wherein the presence of the mixture inside the cells results in target gene silencing, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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7. Claims 1, 2, 4-7, 9, 11-14, 16-18, 20, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al., as applied to claims 1, 2, 4, 9, 11-14, 16-18, 20, and 47 above, in view of Gross et al. (Nucleic Acids Research, 1987, 15: 431-442).

Yang et al. do not teach manganese. Gross et al. teach that RNase III can use manganese for catalytic activity (p. 432 first paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to use manganese for the *in vitro* generation of hsiRNAs by RNase III for a more efficient production of hsiRNAs, with a reasonable expectation of success. The motivation to do so is provided by Gross et al., who teach that replacing magnesium with manganese promotes the cleavage of additional sites in the dsRNA (p.432, first paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in using manganese because the art teaches that manganese can be successfully used for the catalytic activity of RNase III. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. No claim is allowed. No claim is free of prior art.

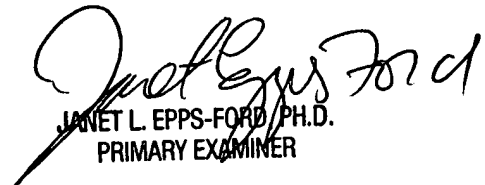
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ileana Popa


JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER